Abstract
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Radiation and the Fetal Epigenome

Radiation-induced bystander effect is a phenomenon where cells not directly exposed to ionizing radiation display a marked enhancement in chromosomal and genomic instability which is thought to result in part from epigenetic changes. There is now accumulating evidence that epigenetic dysregulation during early development is also mechanistically linked to the pathogenesis of adult-onset diseases. Therefore, we seek to determine whether low doses of ionizing radiation during gestation can affect susceptibility to adult-onset diseases by deregulating DNA methylation and/or chromatin structure of the genome. We are using viable yellow Agouti (A^{vy}), Axin fused ($Axin^{Fu}$), and C57/Castaneus mice to test this novel postulate because they are exquisitely sensitive biosensors for environmental agents that alter the epigenome (Dolinoy et al. 2006; Waterland and Jirtle 2003).

Despite a growing consensus on the importance of epigenetics in the etiology of chronic human diseases, the genes most prone to epigenetic dysregulation are incompletely defined. This major deficit in knowledge has severely constrained our ability to systematically define and characterize the imprinted genes and metastable epialleles mechanistically involved in the etiology of human chronic diseases. Therefore, we have implemented an expression microarray approach to identify imprinted genes and metastable epialleles in mice whose methylation and/or chromatin structure and corresponding expression are potentially altered by maternal exposure to a chronic low dose of ionizing radiation during gestation.

The expression microarray approach to identify epigenetically labile genes takes advantage of the unique expression pattern of the A^{vy} metastable epiallele, which we have coined the "Agouti Fingerprint." DNA methylation analysis of the A^{vy} IAP retrotransposon region indicates high variance between isogeneic individuals and low variance among tissue types in individual animals (Dolinoy et al. 2006; Waterland and Jirtle 2003). In addition, microarray analysis demonstrates high variance in *Agouti* RNA levels between isogeneic pseudoagouti (brown) animals and yellow animals coupled with low variance among tissue types in individual animals. Using Affymetrix expression arrays, we have now queried the entire mouse genome for imprinted genes and metastable epialleles that display the Agouti Fingerprint. Approximately 115 of the greater than 40,000 genes on the mouse array display an expression pattern characterized as low inter-tissue variation and high inter-individual variation. This set of genes represents our candidate list of genes potentially modifiable by maternal low dose ionizing radiation. It is imperative that these preliminary expression findings now be confirmed by real time PCR techniques.

References:

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Dolinoy, D.C., Weidman, J.R., Waterland, R.A., and Jirtle, R.L. Maternal genistein alters coat color and protects *Avy* mouse offspring from obesity by modifying the fetal epigenome. *Envir. Health Perspect*. 114: 567-572, 2006.